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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/555,026	01/18/2002	Tadashi Mukai	06854.0011	8884

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EXAMINER	
KRASS, FREDERICK F	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 10/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/555,026	MUKAI ET AL.	
	Examiner	Art Unit	
	Frederick F. Krass	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-45 and 48* is/are rejected.

7)☒ Claim(s) *46 and 47* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Case

All previous rejections are withdrawn.

A new ground of rejection follows infra. Because it was not necessitated by Applicant's amendment, this action is NON-FINAL.

Specification

Applicant is requested to amend the first line of the specification to refer to the claim for priority to PCT/JP00/01722.

Obviousness Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 32-45 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mukai et al (WO 97/48382) in view of Liversidge et al (USP 5,145,684).

The primary reference discloses compositions comprising cilostazol in multi-unit form for sustained release in the stomach. The individual units, or portions of individual units, may be varied so that one part releases the active agent more quickly than the other (see for example the passage bridging p. 7, line 5, to p. 9, line 24), fairly suggesting the administration forms of instant claims 45 and 48. It is silent regarding dispersing fine particles (10um or less) in a dispersing agent.

The secondary reference discloses a method for increasing the bioavailability of sparingly water-soluble drugs by reducing their particle size by micronization, followed by dispersion in a surface modifier (see col. 5, lines 50 et seq.), preferably a surfactant such as sodium lauryl sulfate (col. 5, line 4). Such processing produces dispersions of extremely fine particles (400nm or less). These dispersions may then be dried and incorporated into solid dosage forms (col. 7, lines 53-60). The amount of dispersing agent is preferably 0. 1 to 60 percent by weight, relative to the weight of the drug particle (col. 7, lines 10-20). The reference differs from the instant claims insofar as it does not specifically disclose cilastazol, although it clearly contemplates the use of a wide variety of known pharmaceutical agents as taught at col. 3, lines 38 et seq. The secondary reference also teaches that because of increased bioavailability, drugs so processed have improved onset of drug action and lowered gastrointestinal irritancy (col. 8, lines 3-9).

It would have been obvious to have micronized cilastozol (a sparingly water-soluble drug), then incorporated same into a dispersing agent such as sodium lauryl sulfate for use in the multi-unit dosage

forms of the primary reference, motivated by the desire to provide lowered gastrointestinal irritancy as taught by the secondary reference.

Regarding the secondary reference, it is noted that the instant specification states at p. 3, lines 7-15 that:

> USP 5,145,684 discloses particles consisting essentially of a crystalline drug substance having a surface modifier absorbed on the surface in amount sufficient to maintain an effective average particle size of less than about 400 nm wherein the bioavailability is increased.
>
> But, this USP does not describe increasing the absorption rate at the lower portion of the digestive tract, of slightly soluble drug which exhibits an extremely low absorption rate thereat.

Applicant appears to be stating here that fine particles of drugs in dispersing agents are known from USP 5,145,684, but that one could not have predicted dispersing cilastozol in that manner would provide improved release in the lower digestive tract. The instant claims, however, require only the ability to be released in the lower portion of the digestive tract, not that such release actually occur. Any cilastozol composition is "able" to be released in the lower intestine insofar as it can be formulated into a colon-specific administration form. In other words, ability to provide improved absorption in the lower digestive tract is merely a statement of intended future use which carries no weight in determining patentability. Accordingly, by this reasoning the instant claims would not be adequately distinguished from compositions suggested by the combined teachings of the primary and secondary references, whether the improved lower intestine availability observed by Applicant without the need for further formulation or processing was obtained or not.

Allowable Subject Matter

Claims 46 and 47 are objected to as being dependent on a rejected based claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Mukai et al (WO 97/48382) is specifically concerned with improving the release profile of cilastozol in the stomach. See, for example, the first paragraph of p. 3, and p. 10, lines 6-10. It also recognizes the unpredictability of maintaining adequate blood concentration of cilastozol following release in the digestive tract: see p. 4, lines 4-10. Given these facts, one would not have been motivated to have used an enteric coating (meaning release would not occur until reaching the intestine) as required by the instant claims, particularly in a combined dosage form comprising individual elements having different rates of release. This would, at best, only be an "obviousness to try" situation.

Additionally, Applicant's discovery that incorporating cilastozol having a particle size of 10um or less into a dispersing agent provides unexpectedly improved absorption in the lower intestine would overcome any case of obviousness which might, *purely arguendo*, be established. Note that these unexpected results are considered probative in this instance, whereas they were not in the "Obviousness" section supra, because the instant claims recite specific structural elements – enteric coatings – which circumscribe compositions which actually do release their contents in the intestinal tract, and not merely broadly recited compositions which might release their contents in the intestine at some future time.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frederick F. Krass whose telephone number is 571-272-0580. The examiner's schedule is 9:30AM – 6:00PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Frederick Krass
Primary Examiner
Art Unit 1614